THE INFLUENCE OF RENAL FUNCTION ON HYPERGLYCEMIA AND GLYCOSURIA IN DIABETES MELLITUS.

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The role of the kidney in the production and regulation of glycosuria still remains an unsettled problem. It is generally conceded that the presence of sugar in the urine usually represents an overflow from the blood. This assumption presupposes that the quantity of sugar in the blood is in excess of what the kidneys can tolerate or utilize, thereby causing its excretion. The point at which sugar begins to appear in the urine (threshold value) has not been definitely established. Numerous attempts have been made to ascertain the exact blood-sugar level which leads to glycosuria by means of oral and intravenous administration of glucose, but the results obtained thus far are not concordant. It is certain, however, that the kidneys of a normal individual are usually quite "impermeable" for the quantity of glucose that circulates in the blood even after the ingestion of large amounts of carbohydrates.

Increased Renal Permeability. Certain instances of glycosuria are on record in which an increase in the blood-sugar content above the normal percentage was not present, or rather not demonstrated. These cases have been variously termed "renal diabetes" or "renal glycosuria."[1] The phenomenon revealed by them is usually explained on the basis that the kidneys are more permeable to sugar than normally. In the light of recent work by the author,[2] the evidence adduced in proof of the existence of a renal diabetes or renal glycosuria cannot be regarded as wholly sufficient. It is yet to be determined that in these forms of glycosuria the "percentile" sugar content is the proper index of the actual amount of sugar in the blood.

The results of the investigation referred to point to the probability that the total sugar content of the blood plays the leading part in determining the presence or absence of a hyperglycemia and not its percentile concentration. According to this conception a hyperglycemia (increase in the total sugar content) may be present without showing any increase in the percentage of the blood-sugar. Because of this fact a glycosuria may even occur when the sugar content is apparently not increased. These phenomena appear in certain cases of diabetes mellitus, and the following protocol is offered as an example.[3]

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[1] Lewis, D. S., and Mosenthal, H.: Johns Hopkins Bull., 1916, xxvii, 133.

[2] Epstein, Albert A.: Proc. Soc. Exp. Biol. and Med., 1916, xiii, 67; also, Relation of Hyperglycemia to Glycosuria, Monograph, May, 1916, New York.

Case History.—G. R.; female, aged forty-two years; admitted to the hospital (service of Dr. N. E. Brill) November 18, 1914. Chief complaints of patient: pruritus vulvæ, weakness, loss of weight, polydipsia, and polyuria. Exact date of onset of symptoms not known; but pruritus developed in summer of 1914, lasted a short time, and recurred two months prior to admission to the hospital. The polydipsia and polyuria were noted one month before the return of the pruritus.

Upon physical examination the patient appeared poorly nourished, with cheeks flushed, skin dry, and lips and tongue parched. A distinct acetone odor to the breath was present. Chest examination revealed the presence of a chronic bronchitis. Heart action was poor; no other cardiovascular phenomena. Abdomen lax; liver palpable below free border of ribs on deep inspiration. Marked redness of the vulva and the parts about. Cervix lacerated; uterus enlarged.[4]

On a mixed hospital diet the patient's urine contained from 2.1 to 4.2 per cent. of sugar, containing between 22 and 30 grams of glucose daily.

November 23, 1914, the blood-sugar and the relative blood volume were determined in the morning on a fasting stomach. Directly thereafter the patient was given a test breakfast of 50 grams of glucose in 200 c.c. of coffee. The blood-sugar, relative blood volume, and the urine were examined hourly for a number of hours. The results obtained are tabulated below.

Table I.

Time.	Blood-sugar, per cent.	Urine Quantity, c.c.	 Sugar, per cent.	 Total sugar, grams.
9.30 A.M.	0.152			
10.30 A.M.	0.264	142	5.71	8.11
11.30 A.M.	0.184	62	5.45	3.38
12.30 A.M.	0.164	33	4.00	1.32
1.30 P.M.	0.116	17	1.54	0.26
2.30 P.M.	0.122	14	2.25	0.32
3.30 P.M.	0.138			

On a restricted diet the glycosuria disappeared very rapidly and the blood-sugar dropped to normal. The patient's general condition improved and the symptoms originally complained of were no longer present. The above test was repeated on December 2 and the following results were obtained.

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[3] Epstein, Albert A.: Loc. cit.

[4] It was discovered subsequently that the patient was in the fifth week of pregnancy when she entered the hospital.

TABLE II.

Time.	Blood-sugar, per cent.	Urine		
		Quantity, c.c.	Sugar, per cent.	Total sugar, grams.
9.30 A.M.	0.080			
10.30 A.M.	0.121	47	0.30	0.141
11.30 A.M.	0.140	58	3.04	1.763
12.30 A.M.	0.125	47	4.36	2.049
1.30 P.M.	0.095	12	1.37	0.164
2.30 P.M.	0.076	25	0.30	0.075

The results yielded by the second test are of unusual interest and importance. It appears that the administration of the glucose in the test breakfast gave rise to an intense glycosuria, although the blood-sugar remained practically normal throughout the period of observation. At least the course pursued by the glycemia at this stage of the disease is comparable to that observed in cases of "renal diabetes."

After the subsidence of the glycosuria caused by the test there no longer appeared any sugar in the urine, although the diet was steadily made more liberal. The patient's condition continued to improve. On December 19, when the patient appeared to be in very good health and capable of tolerating liberal amounts of carbohydrates, another test similar to the one above was made, with the object of ascertaining the reaction of the blood and the kidneys to the administration of glucose. The results of this test appear in the table below.

TABLE III.

Time.	Blood-sugar, per cent.	Urine		
		Quantity, c.c.	Sugar, per cent.	Total sugar, grams.
9.30 A.M.	0.073			
10.30 A.M.	0.067	34	0	
11.30 A.M.	0.114	32	4.00	1.260
12.30 P.M.	0.127	98	4.36	4.273
1.30 P.M.	0.085	60	5.33	3.198
2.30 P.M.	.....	52	3.43	1.783

We observe here that the patient's blood-sugar on a fasting stomach reaches a low level, 0.075 per cent. No hyperglycemia is in evidence at any time during the entire test, at the same time that a very pronounced glycosuria is present.

I know of no case of "renal diabetes" in the literature in which so marked a glycosuria is present associated with so low a blood-sugar content. Without a definite knowledge of the antecedent history of this case, and the facts gleamed from the earlier tests, one might regard the case at this stage as an instance of "renal diabetes" or "renal glycosuria." The fact that the ingestion of glucose caused the glycosuria would not necessarily disbar it from this classification. The important feature is the absence of a hyperglycemia. If then the percentile blood-sugar content could be taken as the true index of the amount of glucose present in the blood the conclusion would be warranted that the kidneys of this patient were or had become unusually permeable to sugar.

However, that the absence of hyperglycemia in the second and third tests made on this patient is only apparent and not real is evident from observations made on the blood volume simultaneously with the blood and urine analysis for sugar.[5] The data obtained show that the blood volume had become much increased, and, although the percentage concentration of glucose is low the total amount in circulation is increased throughout the glycosuric period. The increase in the blood volume that had occurred while the patient was under observation is demonstrated by the following results.

TABLE IV.—SHOWING CHANGES IN THE RELATIVE BLOOD VOLUME ON THE THREE TEST DAYS.

	Blood plasma, per cent.			Blood cells, per cent.			Relative blood volume, per cent.		
	Nov. 23.	Dec. 2.	Dec. 19.	Nov. 23.	Dec. 2.	Dec. 19.	Nov. 23.	Dec. 2.	Dec. 19.
9.30 A.M. . .	48.3	55.1	57.5	51.7	44.9	42.5	100.0	115.2	121.6
10.30 A.M. . .	51.8	55.2	60.9	48.2	44.8	39.1	107.4	115.2	132.2
11.30 A.M. . .	53.9	53.2	59.7	46.1	46.8	40.3	112.2	110.6	128.2
12.30 A.M. . .	53.8	56.3	59.9	46.3	43.7	40.1	111.9	118.6	128.9
1.30 P.M. . .	53.8	56.0	58.3	46.2	44.0	41.7	111.9	117.5	123.9
2.30 P.M. . .	56.2	56.0	59.7	43.8	44.0	40.3	118.0	117.5	127.7
3.30 P.M. . ..	54.6	56.3	..	45.5	43.7	..	113.9	118.6	...

These data show very clearly just what has taken place in the circulating blood. Evidently its volume had increased, so that on December 2 and 19 it was found to be decidedly greater than it was at the time of the first examination on November 24. The percentages of sugar found in the blood upon examination are therefore masked by the alteration in the blood volume. Had the blood volume remained unchanged the blood-sugar content would really have been as follows:

TABLE V.—SHOWING THE CORRECTED BLOOD-SUGAR CONTENT ON THE THREE TEST DAYS.

	Blood-sugar		
	Nov. 23. Per cent.	Dec. 2. Per cent.	Dec. 19. Per cent.
9.30 A.M.	0.152	0.092	0.088
10.30 A.M.	0.283	0.134	0.089
11.30 A.M.	0.206	0.166	0.146
12.30 P.M.	0.183	0.147	0.164
1.30 P.M.	0.130	0.112	0.108
2.30 P.M.	0.144	0.090	
3.30 P.M.	0.158		

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[5] The blood variations were determined by means of the simplified hematocrit devised by the author (Jour. Lab. and Clin. Med., 1916, i, 610).

According to my understanding of a hyperglycemia (*i. e.*, increase in the total blood-sugar content[6] these figures represent a definite hyperglycemia, and are compatible with the findings in the urine in the corresponding periods of time.

If we disregard the blood volume changes and their influence on the blood-sugar content in this instance we must draw the conclusion that the kidneys had become more permeable to glucose than they were at the outset, or that they had acquired the ability to eliminate sugar in the absence of a hyperglycemia. (Compare Tables I, II, III.) We would thus have a condition resembling renal glycosuria in a truly diabetic individual.

George Graham[7] records one case of definite diabetes with a relatively low blood-sugar content, and terms the condition "low-level leak-point." This observer, however, has made no control estimations of the blood volume in his case, and hence the interpretation given cannot be accepted as conclusive.

The occurrence of a glycosuria of purely renal origin is, of course, quite possible; but with the evidence which we possess concerning the phenomenon it seems premature to speak of the existence of "renal diabetes" or "renal glycosuria," or to regard the cases recorded in the literature as definite instances of increased renal permeability for glucose.

It appears fairly certain that changes in blood volume occur and that these changes exert an influence upon the concentration of different ingredients. It will therefore be necessary in the future in a consideration of the subject of hyperglycemia to take variations in blood volume into definite account. With the methods which we now possess for estimating blood-sugar and determining the blood volume there ought to be no difficulty in ascertaining whether or not a "renal glycosuria" or "diabetes" represents a condition of increased renal permeability or that such a glycosuria is the result of an actual (but masked) hyperglycemia.

DIMINISHED RENAL PERMEABILITY VS. RENAL TOLERANCE FOR SUGAR. A lessened capacity of the kidneys to eliminate sugar, on the other hand, is frequently encountered. The older observers (Naunyn,[8] v. Noorden[9]) as well as the more recent ones (Allen,[10] Macleod,[11] Graham,[12]) make mention of this condition, and numerous instances of persistent hyperglycemia with slight or no glycosuria are recorded. A number of such cases have come under my observation whose blood upon examination yielded the following results:

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[6] Epstein, Albert A.: Loc. cit.

[7] Proc. Phys. Soc., London, Jour. Phys., 1916, xlix, 46–48.

[8] Der Diabetes Mellitus, 1906, p. 189.

[9] Handb. d. Path. d. Stoffw., 1907, ii, 7 and 9.

[10] Glycosuria and Diabetes, 1913, p. 48.

[11] Diabetes, its Pathology and Physiology, 1913, p. 48.

[12] Loc. cit.

TABLE VI.

Case.	Blood-sugar, per cent.	Urinary sugar, per cent.
1. G. Web.	0.144	0
2. Re.	0.195	0
3. Wur.	0.136	0
4. Str.	0.194	0
5. Lei.	0.154	0
6. Adv.	0.162	0
7. Feu.	0.208	0
8. Lev.	0.132	0
9. Gla.	0.324	0.25
10. Bon.	0.260	0
11. De B.	0.216	0
12. Rab.	0.164	0
13. Rub.	0.188	0
14. Mar.	0.324	0
15. Meh.	0.184	0
16. Fruh.	0.172	0
17. Bry.	0.222	0
18. Kay.	0.132	0
19. Sil.	0.190	0
20. Hor.	0.312	0
21. Pin.	0.196	0
22. Elie.	0.280	0
23. Le.	0.180	0
24. G. Car.	0.264	0
25. Ed. Car.	0.258	0
26. Gin.	0.180	0
27. Sche.	0.200	0

NOTE.—The blood was taken in all the above cases early in the morning, before breakfast, so that the figures represent the blood-sugar content on an empty stomach. The examination of the urine was made on twenty-four-hour specimens, on the same day on which the blood was examined.

The cases presented show varying degrees of hyperglycemia ranging from 0.132 per cent. to 0.324 per cent., without any glycosuria.

It is known that with the approach of coma in diabetes the sugar may disappear from the urine and accumulate in the blood. Clinical and experimental observations of this fact are on record. (v. Noorden,[13] Joslin,[14] Epstein and Felsen,[15] Epstein and Baehr.[16]) Extreme weakness and impaired circulation may also lessen or prevent the excretion of sugar because the kidney function is affected by these conditions.

In febrile states, too, the glycosuria may disappear while the hyperglycemia persists. According to Barrenscheen[17] the diminution or cessation of glycosuria after liberal feeding of oatmeal is due to diminished permeability of the kidneys. The relative infrequency of glycosuria in normal individuals after operative procedures (requiring the use of anesthetics such as nitrous oxide and ether) in whom a definite hyperglycemia develops is attributable to a lessened permeability of the kidneys.[18] The use or administration of a number of drugs and chemicals is known to affect the sugar-secreting power of the kidneys, and the development of a chronic nephritis is regarded as a common cause of the cessation of the glycosuria in diabetes. Thus, many conditions which affect the kidney function may interfere with the glycosuria.

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[13] Loc. cit., p. 3.

[14] The Treatment of Diabetes, 1916, p. 72.

[15] AM. JOUR. MED. SC., to appear August, 1917.

[16] Jour. Biol. Chem., 1916, xxiv, 1.

[17] Biochem. Ztschr., 1912, xxxix, 232.

But, whereas, the advent of a chronic nephritis may be associated with the disappearance of sugar from the urine, the latter need not necessarily be the result of the kidney affection. Very severe grades of renal disease may occasionally be present in diabetes without in any way interfering with sugar elimination. Two such cases have come under my observation, both dying of undoubted uremia.[19] In both the nephritis and the diabetes were of long standing; the glycosuria and hyperglycemia however, followed a course common to ordinary uncomplicated cases. The presence of albumin in the urine of diabetic individuals is very frequent, yet there appears to be no disturbance in the excretion of sugar in consequence of it.

The sugar may disappear from the urine of a diabetic without the intervention of a nephritis. According to Allen:[20] "The action of the sugar itself is held accountable for the diminished permeability of the diabetic kidney, and it would not be surprising if the kidney should acquire habituation to the long-continued hyperglycemia." A study of the blood-sugar and a close analysis of such cases points to the probability that the cessation of the glycosuria is in many of them the result of an altered state of carbohydrate assimilation rather than the sequel of a diminished renal permeability or sugar "habituation," for, we know that when an active disturbance of carbohydrate metabolism is present, causing a hyperglycemia and glycosuria, any interference with the excretion of sugar by the kidneys results in its accumulation in the blood. The disappearance of the glycosuria does not mark the cessation of the diabetes. This is confirmed by the progressive rise in the hyperglycemia. Clinical examples of this condition are furnished by the cases of Lepine,[21] v. Noorden, Joslin,[22] and also those of the author and Felsen.

Under these conditions the blood-sugar may rise to very unusual heights, 1 per cent. and over, the highest being 1.379 per cent. (Joslin[23]). Similar results are encountered in experimental animals after pancreatectomy (Epstein and Baehr[24]).

But this is entirely different from the conditions which exist in cases of diabetes, alluded to above (see Table VI), in which the glycosuria vanishes and a hyperglycemia persists without showing any progressive increase. Liefman and Stern[25] in their researches

[18] Epstein, A. A., Reiss, J., and Branower, J.: Jour. Biol. Chem., 1916, xxvi, 25.

[19] Case L. F.: Incoagulable nitrogen, 0.242 gm. per 100 c.c. serum. Case P. K.: Incoagulable nitrogen, 0.320 gm. per 100 c.c. serum.

[20] Loc. cit.

[21] Rev. de Méd., 1897, xvii, 832.

[22] Loc. cit., p. 72.

[23] Loc. cit., p. 72.

[24] Loc. cit.

[25] Biochem. Ztschr., 1906, i, 299.

on the subject have partly recognized this difference. In order to distinguish between the mechanism which governs the production of a hyperglycemia and that which regulates the glycosuria, they propose the terms "inner" and "outer tolerance" for sugar. The first term applies to the blood-sugar regulation and the ability of the tissues to use it. The second refers only to permeability of the kidneys.[26]

Without some such interpretation the conduct of the blood-sugar in the two types of cases is irreconcilable. Certainly, the term lessened "permeability" of the kidneys for sugar cannot be applied with equal propriety to both. A distinction must be made between the cases in which the disappearance of sugar from the urine results in a progressively increasing hyperglycemia and those in which the cessation of the glycosuria is accompanied by a persistent hyperglycemia which remains fairly constant. There is a clinical difference as well as a pathological one between the two groups: the one indicates failing renal function of a certain type, is rapid in its development, and often signifies the close approach of coma and death; the other is of long duration, often presenting none of the symptoms common to diabetes, and is compatible with good health.

In view of these facts I have applied renal function tests in addition to blood-sugar estimations to a number of cases of diabetes in order to determine the relation of the hyperglycemia and glycosuria to the activity of the kidneys. As stated before, Barrenscheen[27] in studying the influence of oatmeal feeding on the diabetes, found that the resulting decrease in the sugar output was associated with a disturbance in renal function which caused a retention of water and of glucose. Guided by the results of renal tests (lactose and potassium iodide) he came to the conclusion that the oatmeal caused an injury to the glomerulovascular apparatus. His deductions gain support from the fact that the administration of a diuretic, such as theocin, tends to overcome the effect of the oatmeal.

The results obtained in this investigation are therefore of considerable interest and serve to elucidate some of the points under discussion.

Methods. For the determination of renal function, phenolsulphonephthalein was used. Although this substance does not aid in distinguishing different types of renal affections it serves to indicate the presence and extent of functional disorders. An excretion of less than 60 per cent. of the dye in two hours is regarded here as subnormal. The blood-sugar was estimated by means of the microchemical method of the author,[28] and for quantitative analyses of the glucose in the urine, Rudisch solution was employed.

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[26] In the 2 cases studied by Graham (loc. cit.) the phenomenon (hyperglycemia with little or no glycosuria, or "high—level leak—point" as he terms it) is interpreted as being of the "nature of a protective mechanism." But it is difficult to understand the meaning of "protective mechanism." Does it signify diminished renal permeability or altered carbohydrate utilization?

[27] Barrenscheen, H. K.: Loc. cit.

The observations here recorded were carried out on 60 cases. The blood was obtained for analysis early in the morning on a fasting stomach. Directly thereafter the patients received 6 mgs. of phenolsulphonephthalein intramuscularly and then were permitted to drink 2 glasses (16 ounces) of water. The patients voided urine at the end of one and two hours. In certain instances the urine was obtained by catheterization. In a number of cases the examination was repeated, for reasons which will be evident later on.

The cases studied may be grouped as follows:

1. Active cases of diabetes untreated:
    (*a*) Without renal disease.
    (*b*) With renal disease.
2. Active cases of diabetes rendered sugar-free by treatment:
    (*a*) Without renal disease.
    (*b*) With renal disease.
3. Confirmed cases of diabetes which have become sugar-free spontaneously:
    (*a*) Without renal disease.
    (*b*) With renal disease (none encountered).
4. Active cases of diabetes showing diminution or disappearance of the glycosuria, but in reality the condition being much aggravated.

TABLE VII.—GROUP I.—UNTREATED CASES OF DIABETES, WITHOUT NEPHRITIS.

Case.	Blood-sugar, per cent.	Urine. 24-hr. specimen, c.c.	Urine. Sugar, per cent.	Phenolsulphonephthalein. 1st hr., per cent.	Phenolsulphonephthalein. 2d. hr., per cent.	Excretion, total per cent.
23. M. Le.	0.210	3000	2.0	38.0	26.0	64.0
28. Mas..	0.210	2350	4.1	55.0	26.0	76.0
29. Nat.	0.300	2250	5.0	48.0	18.0	66.0
30. Ros.	0.292	2750	4.1	50.0	15.0	65.0
Average	0.253		3.8			68.0
UNTREATED CASES OF DIABETES WITH NEPHRITIS.						
9. Gla.	0.324	..	0.25	23.0	28.0	51.0
22. Elie	0.252	..	0.75	13.0	20.0	33.0
10. Bon.	0.260	..	0.40	29.0	18.0	47.0
21. Pin.	0.248	1325	1.40	27.0	13.0	40.0
Average	0.271		0.70			43.0

The figures tabulated above are representative of the results obtained in a large number of diabetic patients upon whom the tests were made prior to the inception of treatment. The table shows that the range of variation of the hyperglycemia in the two types of cases is approximately the same, but the extent of the glycosuria is strikingly different. Comparison is facilitated by averaging the figures obtained. We thus find that the blood-sugar content in the two groups is 0.258 per cent. and 0.271 per cent.; whereas the concentration of the urinary sugar is 3.71 per cent. and 0.70 per cent., respectively. The phenolsulphonephthalein excretion of these cases seems to parallel the sugar elimination, being considerably lower in the nephritic than in the non-nephritic group, the average for the two groups being 66 per cent., and 43 per cent., respectively.

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[28] Epstein, Albert A.: Jour. Am. Med. Assn., 1914, lxiii, 1667.

It would appear from a comparison of the phenolsulphonephthalein excretion and the sugar output of the cases presented that there is a definite relation between the two functions: that disease of the kidneys interferes with the sugar elimination as well as with that of the dye. In view of the approximate equality of the hyperglycemias in the two types of cases and the marked difference in the glycosuria it would seem likely that the kidneys of the nephritic individuals are less permeable to sugar than those of the non-nephritic cases.

However, it does not necessarily follow that the diminished glycosuria observable in the nephritic cases is the result of the renal disease. In the first place, repeated examinations of the blood-sugar in the nephritic cases fails to show any progression of the hyperglycemia, such as that found in cases in which failing kidney function interferes with the elimination of sugar (see Cases 35 and 36); so that the hyperglycemia observed in these nephritic cases is really not the result of sugar retention due to renal "impermeability." Further, withdrawal of carbohydrates from the diet of these individuals leads to a rapid disappearance of the glycosuria, but the hyperglycemia persists. Reference has also been made to the fact that a very severe nephritis may be present and exert no influence whatever on the intensity of the glycosuria nor on the height of the hyperglycemia.. For example the two cases of this type previously mentioned presented the following results:

Case A. F. Blood-sugar, 0.300 per cent.; urine, 4440 c.c.; sugar, 5 per cent.; total, 222 grams. Phenolsulphonephthalein, 18 per cent.

A. K. Blood-sugar, 0.218 per cent.; urine, 3600 c.c.; sugar, 4.6 per cent.; total, 165.6 grams.

The quantity of sugar found in the blood at any one moment represents the result of three functions: (1) the rate at which sugar is thrown into the circulation; (2) the rate of its utilization by the tissues; (3) the rate of renal excretion. If the supply of sugar to the blood is in excess of tissue requirement, and more than the kidneys can eliminate, it must accumulate in the blood stream. This has been referred to above and will be demonstrated by specific cases presently. If, therefore, a marked hyperglycemia is present which remains constant over a considerable period of time, causing little or no glycosuria (whether a nephritis is present or not), it signifies that a balance has been established between the rate at which sugar is supplied to the blood and its utilization by the tissues. This is supported by the findings in a group of cases without renal disease in which the glycosuria disappeared spontaneously or following treatment, but the hyperglycemia remained persistently high. (See Tables VIII and IX.)

TABLE VIII.—GROUP II.—DIABETIC CASES RENDERED SUGAR-FREE BY TREATMENT: NON-NEPHRITIC.

Case.	Blood-sugar, per cent.	Urine.		Phenolsulphonephthalein.		Excretion, total per cent.
		24-hr. specimen, c.c.	Sugar, per cent.	1st hr., per cent.	2d. hr., per cent.	
25. Ed. Car.	0.258	1560	0	40.0	22.0	62.0
31. A. Mor.	0.178	1250	0	44.0	27.0	71.0
17. Bry	0.222	..	0	40.0	22.0	62.0
16. Fruh.	0.172	3000	0	57.0	21.0	78.0
14. Mar.	0.324	..	0	60.0	15.0	75.0
15. Meh.	0.182	..	0	..	..	69.0
24. G. Car.	0.264	1600	0	54.0	21.0	75.0
11. De B.	0.216	..	0	33.0	23.0	56.0
5. Lei	0.164	2500	0	30.0	29.0	59.0
Average	0.220					67.0

DIABETIC CASES RENDERED SUGAR-FREE BY TREATMENT: NEPHRITIC.

7. Feu.	0.208	..	0	17.0	24.0	41.0
20. Hor.	0.312	..	0	26.0	29.0	55.0
32. Trou.	0.101	900	0	37.0	9.0	46.0
33. J. Wei.	0.213	..	0	28.0	27.0	55.0
Average	0.217					49.0

TABLE IX.—GROUP III.—CONFIRMED DIABETICS WHO HAVE BECOME SUGAR-FREE SPONTANEOUSLY: NON-NEPHRITIC.

Case.	Blood-sugar, per cent.	Urine.		Phenolsulphonephthalein.		Excretion, total per cent.
		24-hr. specimen, c.c.	Sugar, per cent.	1st hr., per cent.	2d. hr., per cent.	
19. Sil.	0.196	1500	0	55.0	19.0	74.0
18. Kay.	0.132	..	0	40.0	30.0	70.0
6. Adv.	0.162	..	0	47.0	17.0	64.0
4. Str.	0.194	2280	0	42.0	18.0	60.0
Average	0.171					67.0

Among the cases presented in Table VIII there are four with evidences of renal disease. The only difference observable between these latter and the non-nephritic cases is in the amount of phenolsulphonephthalein excreted. The non-nephritic cases manifest a high blood-sugar content without a glycosuria and the phenolsulphonephthalein elimination is normal. The group of spontaneously recovered cases is comprised of individuals who were known to have had diabetes but who made no special effort to control the disease. From the stand-point of the glycosuria these cases might be classed as mild or moderate. However, the blood-sugar in them is high, but not to the same extent as in those which have been rendered sugar-free by treatment. This may be due to a difference in the duration of the sugar-free period. The functional activity of the kidneys in these cases is perfectly normal.

Two deductions appear admissible from these results: (1) that an increased blood-sugar content may be present in diabetic individuals without giving rise to glycosuria even in the absence of renal disease; (2) that the hyperglycemia in the nephritic individuals is no greater than it is in the non-nephritic.

That the hyperglycemia observed in the above cases is not the result merely of a lessened renal permeability, but that of some alteration in the supply and utilization of sugar, is shown by the relative constancy of blood-sugar content which is observed when the examinations are frequently repeated. An illustration of this fact is found in the following cases:

TABLE X.

Case.	Date.	Blood-sugar, per cent.	Urine-sugar.
2. Re.	Jan. 29, 1916	0.195	0
	Nov. 1, 1916	0.220	0
	Nov. 11, 1916	0.180	0
5. Lei.	July 13, 1916	0.154	0
	July 31, 1916	0.148	0
	Aug. 5, 1916	0.162	0
10. Bon.	April 8, 1916	0.260	0
	April 9, 1916	0.244	0
	April 10, 1916	0.250	0
	April 11, 1916	0.260	0
	April 12, 1916	0.210	0
	April 13, 1916	0.200	0
	April 14, 1916	0.220	0
	April 16, 1916	0.240	0
22. Elie.	June 19, 1916	0.280	0
	July 8, 1916	0.320	0
	July 15, 1916	0.320	0

The above cases serve as an illustration of the condition which is encountered in certain cases of diabetes—namely, a persistent hyperglycemia which remains at a constant level. There is no glycosuria, notwithstanding the fact that the kidneys functionate normally in all other respects. From what has been said before we must conclude that a rearrangement of some sort has taken place by which a balance between the supply of sugar to the blood and its utilization by the tissues is constantly maintained. Undoubtedly, the kidneys take part in this process, as other organs do, so that the absence of sugar from the urine does not indicate a lessened permeability (in the sense of inability to eliminate glucose or an active interference with its excretion), nor does it signify "habituation" of the kidneys to the hyperglycemia, for that alone would not be capable of maintaining the blood-sugar content at a constant level.

We must assume, therefore, that the hyperglycemia without a glycosuria which we find in these cases represents a condition in which the supply of sugar is appropriate to the utilization and does not exceed it. The acquired "tolerance" of the kidneys for the hyperglycemia in this sense constitutes a "protective mechanism" (see footnote 26, p. 110) and is different from the mechanism ordinarily understood in the term "lessened permeability."

When the supply of sugar to the blood exceeds the rate of its utilization by the tissues the result is a hyperglycemia. What actually happens when the kidneys fail to excrete the excess is that it accumulates rapidly in the blood and the hyperglycemia mounts progressively. This is illustrated by the cases already referred to (Lepine, v. Noorden, etc.), and the experiments on animals (Epstein and Baehr) mentioned above.

It also has been pointed out that the presence of renal disease and reduced phenolsulphonephthalein excretion may be associated in diabetes, with a marked hyperglycemia and slight glycosuria, and that the latter is not necessarily the result of the nephritis. The question therefore arises concerning the nature of the renal disturbance which is capable of interfering with the glucose elimination, in consequence of which the liberated and unused sugar accumulates in the blood. Reference has been made to Barrenscheen's observations on the effect of oatmeal on the sugar secreting function of the kidneys. The disturbance produced is evidently of a circulatory nature. This is supported by the tests with lactose and potassium iodide instituted by him and by the salutary effect of diuretics upon the disturbance.

The following protocols are therefore of special interest in this connection, because they demonstrate the role of the kidneys in the regulation of the hyperglycemia and glycosuria in diabetes. They indicate, furthermore, that "lessened permeability" is probably identical with failing renal function of a type which may react to therapeutic measures.

GROUP IV.

Case 35.—A. K.; male; aged sixty-three years; suffering from diabetes mellitus for eighteen years. One week before coming under observation he developed a thrombosis of the femoral artery. Upon examination it was found that the patient had a chronic endocarditis and arteriosclerosis. The urine was small in amount (daily output about 900 c.c.), highly concentrated, and contained a moderate amount of albumin, numerous casts, and some blood cells. The sugar output ranged from 2.0 per cent. to 3.5 per cent. The blood-sugar varied between 0.220 and 0.260 per cent.

Dietary restriction (modified Allen regime) caused a prompt disappearance of the glycosuria. The patient's condition improved and he was gradually allowed more food. Two weeks after the first observation, when the patient was permitted to sit in a chair, it was noticed that the quantity of urine passed became diminished (660 c.c. per day). It remained sugar-free, but the amount of albumin and formed elements increased. The heart action appeared much weaker, but there was no evidence of cardiac enlargement. The healthy extremity showed slight edema. The blood examined at this time showed a hyperglycemia of 0.412 per cent.

It was evident that the patient at this stage was receiving more carbohydrate than he could tolerate, and because of the circulatory disturbance, which also affected the kidneys, no sugar appeared in the urine. Cardiac stimulation was resorted to (spartein sulphate and infusion of digitalis), with very prompt response in the pateint's condition. The heart action improved; the quantity of urine rose to 1500 c.c. Sugar appeared in the urine (2.2 per cent.) and the blood-sugar dropped to 0.200 per cent.

Case 36.—A. M.; female, aged forty-two years. Came under observation February 16, 1916, with a history of menorrhagia and diabetes mellitus. Patient stated that when the urine was first examined (some time in January) it contained over 10 per cent. of glucose. The patient complained of the usual symptoms, particularly of the polydipsia and the pruritus vulvae, both of which were observed one month prior to the date of consultation. Upon examination the patient appeared emaciated, weighing 110 pounds (usual weight 139 pounds). The skin and mucous membranes were dry. Tongue heavily coated; acetone odor to the breath. Heart action rapid (110 beats per minute); sounds fairly good; no murmurs. Pulses small and soft; blood-pressure 112 systolic and 80 mm. diatolic (Merser apparatus). Abdomen lax; liver not enlarged. Marked hyperemia of the vulva; uterus enlarged; tumor mass pálpable in the posterior wall.

The patient was put on a restricted diet: 500 grams of 5 per cent. vegetables, black coffee, broths, and small amounts of whisky, 1 to 2 ounces daily. This diet was kept up until the patient became sugar-free, and then gradual additions of other foodstuffs were made.

The clinical course pursued by the patient during the first period of observation (February 16 to March 7), was very favorable. Although there occurred a progressive loss in weight, there seemed to be general improvement. The symptoms originally complained of disappeared and the patient experienced a feeling of well-being. The changes which took place in the blood and urine are recorded in Table XI.

February 17, the first day of observation, the patient eliminated 2000 c.c. of urine, containing 1.2 per cent. of glucose. The blood-sugar was 0.220 per cent., and the phenolsulphonephthalein excretion was 74 per cent. in two hours. March 4 another phenolsulphonephthalein test was made and the excretion was normal (71 per cent, in two hours), although the blood-sugar was 0.178 per cent., and the urine was sugar-free. In other words, the hyperglycemia which remained was not associated with any disturbance of renal function.

TABLE XI.—CASE 36.

Date.	Urine.		Acetone.	Diacetic acid.	Blood-sugar, per cent.	Alveolar CO₂.	Phenolsulphonephthalein excretion.			Remarks.
	Quantity. c.c.	Sugar. per cent.					1st hr.	2d hr.	Total.	
							p. c.	p. c.	p. c.	
Feb. 16, 1916	S.S.	+	+++	+++						
" 17, 1916	2000	1.2	++	++	0.220	..	46	28	74	
" 18, 1916	1500	0.8	++	+						
" 19, 1916	1875	0.6	+	0						
" 20, 1916	1575	0.55	+	++						
" 21, 1916	1950	0	+	0						
" 22, 1916	1600	0	VFT.	0						
" 23, 1916	1375	0	+	0						
" 24, 1916	1250	0	VFT.	0						
" 25, 1916	1200	0	VFT.	0						
" 26, 1916	1600	0	VFT.	0						
" 27, 1916	1200	0	+	0						
" 28, 1916	1400	0	+	0						
" 29, 1916	2150	0	VFT.	0						
Mar. 1, 1916	1600	0	++	0						
" 2, 1916	1125	0	+	0						
" 3, 1916	850	0.7	+	0	0.196					
" 4, 1916	1250	0	+++	0	0.178		44	27	71	
" 5, 1916	750+	0	FT.	0						
" 6, 1916	2725	0	VFT.	0						
" 7, 1916	1200	0.55	+	0	0.182					
June 7, 1916	1200	0.25	+	0	0.284	5.6				
" 8, 1916	1120	0	+	FT.						
" 9, 1916	840+	0.43	Tr.	0	0.268	6.0			48	
" 21, 1916	1080	0.2	0	..	0.288	5.1				
" 22, 1916	990	0	0	0	0.324	3.2				
" 25, 1916	1020	0	0	0	0.272					
July 4, 1916	690	0	0	0	0.166	4.2	..	..	31	Edematous.
" 5, 1916	8000	0	0	0	..	..	..	..	..	Inf. digitalis.
" 6, 1916	3500	0	0	0	0.356	..	..	..	..	Edema absent.
" 7, 1916	2400	0.5	+							
" 10, 1916	1980	2.5	++	Tr.						
" 11, 1916	960	2.2	++	+						
" 12, 1916	1320	2.0	++	+						
" 13, 1916	1410	2.0								
" 19, 1916	1500	1.00								
" 21, 1916	1650	1.1	++	0	0.206	3.9			71	

+ = decided reaction. VFT. = very faint trace. FT. = faint trace. Tr. = trace. Inf. = infusion. S.S. = single specimen.

In the interval between March 7 and June 7 the patient was seen infrequently and definite observations could not be made. June 7 the patient returned and appeared to be in very poor condition. The urine contained only 0.25 per cent. of glucose, a trace of acetone, and no diacetic acid. The blood-sugar, however, was 0.284 per cent., the highest figure yet attained in this case. On the following day the urine was again sugar-free, but a day later a small quantity of sugar reappeared (0.43 per cent.). The blood-sugar taken then was 0.268 per cent., and the phthalein excretion was only 48 per cent. in two hours, hence much lower than in the previous test. It is evident from this observation that there was a retention of sugar at the time, occasioned by defective function, and consequent decrease in renal permeability.

A slight glycosuria alternating with a sugar-free state continued until June 20. The blood-sugar remained at approximately the same high level. In view of the patient's very low tolerance for carbohydrates (in fact for any food) it appeared advisable to attempt fasting. The result of this procedure was an aggravation of existing conditions. The urine became free from sugar and ketone bodies, but the blood-sugar rose to 0.324 per cent., a still higher level than previously observed. The acidosis also increased, as shown by the alveolar CO_2, which dropped to 3.2 per cent. (Frederici apparatus).

A further rise in the hyperglycemia showed definite progression of the diabetic process, notwithstanding the fact that the urine was sugar-free. The fasting was therefore interrupted. A small quantity of 5 per cent. vegetables was allowed, together with 500 c.c. of milk and two ounces of whisky. Because of the increasing acidosis, bicarbonate of soda (4 grams t. i. d.) was administered. As a result of this treatment the patient's condition seemed to improve. The urine remained free from sugar and acetone and the blood-sugar dropped to 0.272 per cent. It is noteworthy that the daily output of urine in this period has been small, particularly as the thirst and polydipsia were pronounced.

The existing pathological conditions became apparent from the course of events in the next period of observation (July 3 to 21). July 3, contrary to instructions, the patient took a lengthy automobile ride. Before the completion of the trip the patient suddenly became very faint, and upon her return it was found that she seemed swollen all over. A very pronounced general anasarca developed in the next twelve hours. The heart action was slow (48 beats per minute) and feeble. The respirations were slow (12 per minute) and sighing in character. The patient was very drowsy, but responded to questions when aroused.

The urine was sugar-free and did not contain any ketones. The blood-sugar was only 0.166 per cent. The phthalein excretion was 34 per cent. in two hours. The latter, of course, was in keeping with the clinical phenomena, *i. e.*, reduced urinary excretion and the edema, but the relatively low hyperglycemia appeared to be paradoxical. The absence of glycosuria, because of deficient renal permeability, should have caused a retention of sugar in the blood, and hence a greater hyperglycemia. The reason for this discrepancy appears in the developments of the next few days.

Following the therapeutic indications at this stage the bicarbonate of soda was stopped, and the infusion of digitalis, in half-ounce doses, every three hours was administered. The result was most remarkable. In the ensuing twenty-four hours the patient eliminated 8000 c.c. urine, which was free from sugar, acetone, and diacetic acid, and the day following 3500 c.c. of a like urine was passed. The edema disappeared entirely. The blood-sugar examined on the morning of July 6 showed the high figure of 0.356 per cent. The blood-pressure, systolic, rose to 128 mm. The heart action was more forcible and the pulse-rate 68 per minute. With the improvement in renal secretion, sugar reappeared in the urine, at first 0.5 per cent. (July 7), rising gradually to 2.5 per cent. (July 10). Subsequently it diminished slowly, and on July 21 the glycosuria was only 1.1 per cent. The blood-sugar on that day was only 0.206 per cent. The phthalein test showed again a normal excretion (71 per cent. in two hours).

Thus it appears that during the period of anasarca the lowered hyperglycemia was due to abstraction of sugar from the blood by the edema fluid. With the increased diuresis and the subsidence of the edema the surplus sugar was returned to the blood. Sugar did not appear in the urine until the function of the kidneys improved, and the glycosuria became progressively more intense as renal activity increased. Following the elimination of the retained sugar the hyperglycemia diminished, so that finally when the renal function returned to normal (July 21) we find moderate glycosuria with a corresponding hyperglycemia, comparable to that observed on the day of the first test (February 17).

The above cases (unlike those of Groups 2 and 3, *vide supra*) show that interference on the part of the kidneys with elimination of sugar causes a retention of this substance in the blood, and hence a progressively increasing hyperglycemia. Although we have no conclusive evidence of the exact nature of the renal disturbance which affects the glycosuria and hyperglycemia in this manner, the associated circulatory disturbances make it seem probable that the derangement in the kidneys is of circulatory origin analogous to the condition found after feeding oatmeal (Barrenscheen). The prompt manner in which these cases react to cardiovascular stimulation, with an increase or reappearance of the glycosuria and a fall in the hyperglycemia, makes this deduction all the more likely.

These observations are of importance not only in showing us a phase of kidney function which influences the hyperglycemia and glycosuria, but also because the diminution or cessation of glycosuria in diabetes mellitus, which is accompanied by a progressively increasing hyperglycemia, affects the prognosis and constitutes an important indication for certain therapeutic measures.

We thus encounter two types of cases in diabetes: one in which the disappearance of the glycosuria is associated with a definite retention of sugar in the blood, due to failing kidney function (lessened permeability), which is probably of circulatory origin; the other in which the cessation of the glycosuria is not the result of renal interference. In this latter group the hyperglycemia may persist, but it remains constant—at least it shows no progression. That this is due to a rearrangement of the carbohydrate metabolism, whereby the plane of sugar utilization becomes elevated ("inner tolerance" of Liefman and Stern or "protective mechanism" of Graham), and not due to a lessened renal permeability, is gleaned from the conduct of such cases under special conditions of nutrition, Since the introduction of the fasting method of treatment of diabetes we have found that the ordinary uncomplicated cases (particularly those of recent origin) show that the disappearance of glycosuria is accompanied by a rapid fall in the blood-sugar, often reaching the normal level. In the group of cases mentioned above (Group 2), fasting reduces the hyperglycemia somewhat, but does not, as a rule, bring it back to normal. In a small proportion of cases considerable reduction in the hyperglycemia may thus be obtained. Macleod mentions one case[21] in which the blood-sugar decreased from 0.183 per cent. to 0.107 per cent., after rigid dietary control. I have found among my cases thirteen instances of reduced hyperglycemia following adequate dietary management, ranging over varying periods of time (see Table XII).

In most instances, however, the hyperglycemia persists long after the disappearance of the glycosuria, notwithstanding fasting and prolonged dietary restrictions.

TABLE XII.

Case.	Date.	Blood-sugar, per cent.	Urine-sugar.
6. Adv.	July 17, 1916	0.162	0
	July 26, 1916	0.066	0
	Aug. 30, 1916	0.098	0
19. Sil.	May 31, 1916	0.196	0
	June 19, 1916	0.115	0
	July 3, 1916	0.080	0
4. Str.	July 16, 1916	0.194	0
	July 30, 1916	0.094	0
	Sept. 8, 1916	0.116	0
	Sept. 21, 1916	0.105	0
32. Trou.	Oct. 28, 1915	0.164	0
	Aug. 24, 1916	0.101	0
25. Ed. Ca.	Jan. 3, 1916	0.300	0
	Nov. 7, 1916	0.194	0
	April 17, 1916	0.258	0
	Aug. 23, 1916	0.162	0
15. Meh.	June 6, 1916	0.182	0
	Aug. 15, 1916	0.100	0
7. Feu.	June 19, 1916	0.208	0
	Aug. 30, 1916	0.112	0
	Sept. 25, 1916	0.110	0
16. Fruh.	July 17, 1916	0.172	0
	Aug. 16, 1916	0.136	0
5. Lei.	July 10, 1916	0.164	0
	Sept. 2, 1916	0.142	0
	Sept. 8, 1916	0.104	0
	Sept. 28, 1916	0.103	0
27. Sche.	Nov. 6, 1914	0.200	0
	May 15, 1916	0.075	0
2. Re.	Jan. 15, 1916	0.260	0
	Jan. 29, 1916	0.195	0
	Nov. 11, 1916	0.180	0
21. Pin.	April 1, 1916	0.248	0
	April 8, 1916	0.196	0
34. Toc.	Sept. 19, 1915	0.190	0
	Sept. 16, 1916	0.109	0

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[21] Macleod, J. J. R.: Loc. cit.

SUMMARY AND CONCLUSIONS. 1. A condition simulating renal diabetes, *i. e.*, a glycosuria without hyperglycemia, may occur in diabetes mellitus. This is brought about by an increase in blood volume which reduces the concentration of the blood-sugar, and the consequent fall in its percentage masks the hyperglycemia. In order, therefore, to prove the existence of a true renal diabetes it is necessary to show that the total sugar content of the blood is not increased above normal.

2. Hyperglycemia without glycosuria is of frequent occurrence in diabetes mellitus. When sugar is absent from the urine a persistent hyperglycemia which remains constant or does not show progression indicates an altered state of carbohydrate metabolism in which a balance is established between the supply of sugar to the blood and its utilization by the tissues on a higher plane than that found normally. This is interpreted as a condition of increased "tolerance" of the kidneys for sugar and not that of "lessened permeability."

3. Renal disease (true nephritis) need not interfere with the elimination of sugar. The cessation of the glycosuria in diabetes mellitus when a nephritis supervenes is not necessarily the result of the kidney affection. Increased tolerance of the kidney for sugar may exist when a nephritis develops. The two conditions may be synchronous or coincident.

4. Lessened permeability of the kidneys, *i. e.*, interference with the excretion of sugar in the course of an active diabetes, leads to the progressive accumulation of sugar in the blood. The glycosuria may diminish or disappear entirely. This clinical complex portends the approach of coma and appears to be due to a circulatory disturbance of the kidneys associated with a general cardiovascular asthenia. The administration of appropriate medication may overcome the disorder. Improvement manifests itself by reappearance of the glycosuria, with a consequent fall in the hyperglycemia. The development of an anasarca may cause a fall in the percentile blood-sugar content and thus conceal the retention of sugar. This is due to the abstraction of sugar from the blood by the edema fluid. The subsidence of the anasarca causes a return of the hyperglycemia.

5. Testing the kidney function by means of phenolsulphonephthalein in diabetes mellitus is a useful procedure. It aids in understanding the relation of the hyperglycemia to glycosuria. It is particularly helpful in those cases in which a fall in the urinary sugar is associated with a rise in the blood-sugar, thus yielding confirmatory evidence of the fact that the elimination of glucose is interfered with.

I wish to acknowledge my thanks to Dr. Joseph Reiss for technical assistance in the work.